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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/699,030	10/26/2000	Shiy Kumar	030516.0029CON1	3324

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EXAMINER
FREDMAN, JEFFREY NORMAN

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 09/15/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/699,030	KUMAR ET AL.	
	Examin r	Art Unit	
	Jeffrey Fredman	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13 and 18-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *5-8 and 10-13* is/are allowed.

6)☒ Claim(s) *1-4,9 and 18-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on July 21, 2003 has been entered.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 3 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Evangelista et al (Anal. Biochem. (1996) 235:89-97).

Evangelista teaches a compound of formula (I) (A-B-C) with a cyanine dye which meets the structural requirements of A, a linker of more than 10 atoms in length as required by B, and attached to the 5 position of dUTP, which has a triphosphate attached (page 91, figure 1). It should be noted, that because the attachment is at the 5 position, dUTP and dTTP yield identical structures.

Evangelista does not teach a structure where this compound is a dideoxynucleotide.

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to modify the labeled deoxynucleotide of Evangelista into a dideoxynucleotide since Evangelista notes "Fluor-labeled deoxynucleotide triphosphates (dNTPs) or dideoxynucleoside triphosphates (ddNTPs) are employed in nonradioactive DNA sequencing techniques such as those developed by Prober et al (ref omitted) and Ansorge et al (ref ommitted) as well as for incorporation into hybridization probes (ref omitted). Fluorescent ddNTPs have also been used as terminal deoxynucleotidyl transferase substrates to label single (ref omitted) and double stranded DNA (ref omitted) (page 89, column 1, last sentence to page 89, column 2)". An ordinary practitioner would have been motivated to alter the dNTP dyes of Evangelista into ddNTP dyes in order to permit nonradioactive DNA sequencing, hybridization probe or terminal transferase methods to be used as expressly taught by Evangelista. An ordinary practitioner would have had a very high expectation of

success since it is routine to make both dNTP and ddNTPs with the same label as discussed by Evangelista on page 89, column 2. It would have been further obvious to utilize the ddNTP resulting from this synthesis in a DNA sequencing method to yield a DNA which comprises the ddNTP.

5. Claims 1-3, 9, and 18-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Evangelista et al in view of Tabor et al (U.S. Patent 5,614,365).

Evangelista teaches a compound of formula (I) (A-B-C) with a cyanine dye which meets the structural requirements of A, a linker of more than 10 atoms in length as required by B, and attached to the 5 position of dUTP, which has a triphosphate attached (page 91, figure 1). It should be noted, that because the attachment is at the 5 position, dUTP and dTTP yield identical structures. Evangelista further notes "Our DNA labeling results indicate that the distance provided by the 10-atom spacer arm between the pyrimidine ring and the rather bulky cyanine label is sufficient to allow base pairing between the deoxyadenosine and deoxyuridine at the ends of the DNA fragments (page 97, column 1)".

Evangelista does not teach the use of a modified thermostable polymerase nor does Evangelista teach placement of the reagents into a kit.

Tabor teaches the use of modified thermostable polymerases in DNA sequencing reactions (column 5, lines 38-58). Tabor further teaches placement of the reagents into a kit (column 9, lines 57-62).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the fluorescently labeled ddNTPS which

are made obvious by Evangelista into a kit with the modified thermostable polymerases of Tabor since Tabor notes "By modification of these enzymes using methods shown below, those in the art can now modify any desired thermophilic DNA polymerase to make it incorporate dideoxynucleotides more efficiently. Such enzymes will be superior to those existing in the present day for DNA sequencing both in automated machines and in manual sequencing, especially in procedures known as cycle sequencing (column 5, lines 46-53)". An ordinary practitioner would have been motivated to form a kit with ddNTPs as made obvious by Evangelista for the improved sensitivity of the dyes (page 96, column 2) as shown by Evangelista and for the use of a superior enzyme as expressly taught by Tabor. An ordinary practitioner would have been motivated to form a kit since with the use of a kit, one need not purchase gram quantities of multiple reagents, each of which is needed in only microgram amounts, when beginning a series of experiments. Further, the kit format saves money and resources by dramatically reducing waste. The other advantage provided in a kit is quality control.

6. Claims 3, 4 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Evangelista in view of Haralambidis et al (Nucleic Acids Research (1987) 15(12):4857-4876).

Evangelista teaches a compound of formula (I) (A-B-C) with a cyanine dye which meets the structural requirements of A, a linker of more than 10 atoms in length as required by B, and attached to the 5 position of dUTP, which has a triphosphate attached (page 91, figure 1). It should be noted, that because the attachment is at the 5 position, dUTP and dTTP yield identical structures. Evangelista further notes "Our DNA

labeling results indicate that the distance provided by the 10-atom spacer arm between the pyrimidine ring and the rather bulky cyanine label is sufficient to allow base pairing between the deoxyadenosine and deoxyuridine at the ends of the DNA fragments (page 97, column 1)".

Evangelista does not teach the specific linkers of claim 4.

Haralambidis teaches a linker (page 4860, figure 1) which is identical to the fourth claimed linker of claim 4, where the linker links to a nitrogen, as occurs in the structure of Evangelista.

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the dye labeled compound rendered obvious by Evangelista with the linker of Haralambidis since Haralambidis states "In this paper we have described a method for the synthesis of C-5 substituted deoxyuridine nucleosides, with the substituent carrying a masked primary aliphatic amino group. This method is exceptionally mild and gives the desired compound is high yield (page 4874)". Haralambidis further notes "It was found that oligonucleotides carrying a long (11 atom) linker arm to the fluorescein hybridize more efficiently to mRNA than those carrying a short (4 atom) arm (abstract, page 4857)". An ordinary practitioner would have been motivated to utilize the long linker arm of Harambidis in the synthesis of the cyanine dye of Evangelista for the expressly stated benefits of mild conditions, high yield and efficient hybridization.

Allowable Subject Matter

1. Claims 5-8 and 10-13 are allowed.

2. The following is a statement of reasons for the indication of allowable subject matter: These claims are drawn to compounds with specific structural formula which are not taught or suggested by the cited prior art such as Evangelista.

Response to Arguments

3. Applicant's arguments filed July 21, 2003 have been fully considered but they are not persuasive.

Applicant reiterates the argument that ddNTPs would not be used in the applications described in Evangelista. This argument is incorrect since Evangelista clearly envisions the use of the labeled nucleotides in automated sequencing type assays (see page 94, column 1). Such assays routinely use labeled ddNTPs for labeling. So when Evangelista teaches the label and suggests the use of the label in sequencing type reactions, this is a direct suggestion to make labeled ddNTPs.

Applicant then argues that Evangelista does not teach formation of a kit with four different ddNTPs for sequencing. With regard to claims 3 and 9, this argument is not relevant since those claims do not include this limitation. With regard to the remaining claims, these are rejected under Evangelista in view of Tabor. Tabor clearly shows the use of four ddNTPs in sequencing reactions (see among extensive examples, column 10, lines 29-31 where Tabor teaches the use of four different terminators). Therefore, the entire line of argument fails because it is not directed at the rejection, which is the

combination of Evangelista and Tabor, not Evangelista alone. Tabor clearly teaches four ddNTPs and it is Tabor combined with Evangelista that renders the claim obvious.

4. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, specific motivation of Evangelista and Tabor is provided in the rejection as Evangelista notes "Fluor-labeled deoxynucleotide triphosphates (dNTPs) or dideoxynucleoside triphosphates (ddNTPs) are employed in nonradioactive DNA sequencing techniques such as those developed by Prober et al (ref omitted) and Ansorge et al (ref ommitted) as well as for incorporation into hybridization probes (ref omitted). Fluorescent ddNTPs have also been used as terminal deoxynucleotidyl transferase substrates to label single (ref omitted) and double stranded DNA (ref omitted) (page 89, column 1, last sentence to page 89, column 2)".

5. As for the slight argument regarding secondary considerations, specifically the assertion of failure by others, no evidence of such failure, or any other secondary consideration whatsoever, is presently on the record.

6. In response to applicant's argument based upon the age of the references, contentions that the reference patents are old are not impressive absent a showing that

the art tried and failed to solve the same problem notwithstanding its presumed knowledge of the references. See *In re Wright*, 569 F.2d 1124, 193 USPQ 332 (CCPA 1977).

Applicant concludes by attempting to denigrate the statement of Evangelista that labeled ddNTPs are useful in sequencing when Evangelista's entire paper is devoted to making fluorescently labeled nucleotides, his very abstract discusses verifying the ability of the compounds made for use as polymerase substrates and where on page 94, column 1, Evangelista expressly identifies sequencing as one of the uses of fluorescently labeled nucleotides. This attempt is not persuasive and the rejections are maintained.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is 703-308-6568. The examiner can normally be reached on 6:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 703-308-1119. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Jeffrey Fredman
Primary Examiner
Art Unit 1634